THE EFFECTS OF LOCAL SUPRALETHAL IRRADIATION ON RENAL FUNCTION

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

FOREWORD
(Nontechnical summary)

In man, radiation nephritis is associated with profound deterioration in kidney function. It occurs in 20 percent of patients who have received cumulative doses exceeding 2300 rads in less than 5 weeks to one or both kidneys. In most cases, the signs and symptoms of this disorder are not evident for 2-3 months after radiation exposure. At that time the damage is irreversible. There is little information available concerning this so-called latent period; that is, the period between the time of exposure and the development of the symptoms. It is important to determine what physiologic alterations occur during this period since early diagnosis may result in more satisfactory treatment for the affected individual. The purpose of this study was to determine the early effects of radiation on kidney function.

By a surgical procedure, the urinary bladders of dogs were divided into two halves called hemibladders which permitted the separate collection of urine from each kidney. Then the left kidney of each dog received 2000 rads of x irradiation. Renal function was determined from collections of urine obtained at specific times separately from each hemibladder while the dog stood quietly in a sling. In this way the effects of radiation on the function of the left kidney were compared to the normally functioning right control kidney. Studies were performed at a preirradiation time, on day 1 and at 7-day intervals postirradiation for a total of 56 days.

The information obtained in the present study indicates that ionizing radiation reduces the ability of the proximal tubule of the nephron to reabsorb sodium within a day of exposure to radiation. This effect became more marked throughout the time of

the study. Further, 3-4 weeks following exposure, urine collected from the irradiated kidney was half as concentrated as the urine collected from the control kidney. This suggests that another early effect of radiation was to reduce the ability of the collecting duct of the nephron to conserve solute-free water.

ABSTRACT

Clearance studies were performed in 16 dogs with surgically formed hemibladders to evaluate the intrinsic renal effects of 2000 rads of x rays administered as a single dose to the left kidney. These studies were conducted under conditions of water diuresis in 10 dogs on days 1, 7 and 14 postexposure. Additional studies were performed 21 and 28 days after exposure in eight of these dogs and 56 days later in four. Six dogs were studied under conditions of osmotic diuresis at all of these intervals.

While the glomerular filtration rate (GFR) appeared to remain constant throughout the 56 days of this study, abnormalities in renal tubular function were evident within 24 hours after irradiation. In water diuresis, free water clearance (C_{H_2O}) was significantly greater 1 day after exposure, averaging 0.88 ± 0.23 ml/min (SE) from the control kidney (CK) and 1.34 ± 0.31 ml/min from the irradiated kidney (IK) ($p < 0.005$). These differences became greater over the intervals studied and were independent of changes in GFR. Fractional excretion of sodium was also greater from the IK within a day of exposure, averaging 0.37 ± 0.11 percent from the CK and 0.54 ± 0.18 percent from the IK ($p < 0.005$). Such differences persisted in the same degree throughout the interval of the study. When vasopressin was infused, urine flow (V) fell significantly at all intervals studied postirradiation. However, V was significantly greater 24 hours after radiation exposure, averaging 0.36 ± 0.08 and 0.54 ± 0.10 ml/min from the CK and IK respectively ($p < 0.001$). This difference in V correlated well with a marked increase in the excretion of total solute and sodium. By day 14, urine flow from the irradiated kidney was not different from the control kidney. Twenty-eight days following exposure, V from the IK tended to be greater than from the CK. These differences

were associated with a significant decline in negative free water clearance ($T^C_{H_2O}$) from the IK (0.30 ± 0.08 ml/min) when compared to the CK (0.52 ± 0.08 ml/min, $p < 0.01$).

The tubular maximum for $T^C_{H_2O}$ ($Tm^C_{H_2O}$) was determined in six dogs that were studied while undergoing a brisk osmotic diuresis and being infused with vasopressin. There was a significant decline in $Tm^C_{H_2O}$ 21 days after exposure which became more marked by day 28, averaging 1.18 ± 0.10 ml/min from the CK and 0.015 ± 0.13 ml/min ($p < 0.001$) from the IK.

When urine was collected 18-24 hours after complete food and water deprivation, no differences were seen in osmolality until day 21. By day 28, osmolality of urine collected from the IK was half that obtained from the CK, averaging 930 ± 148 and 1898 ± 259 mosmol/liter, respectively.

Thus the earliest effects of radiation are related to the ability of the proximal tubule to reabsorb sodium and are manifested by both an increase in the fractional and absolute excretion of sodium within 24 hours of exposure, which continues throughout the interval of the study, and by a marked increase in the excretion of C_{H_2O} within a day of exposure, which becomes greater with time. Approximately 3 weeks postexposure, but before GFR declines, the concentrating segment of the nephron is impaired. These studies suggest that renal tubular injury is the major early effect of radiation.

I. INTRODUCTION

In the late 1920's ionizing radiation was shown to cause renal impairment when administered locally as a single supralethal dose.[9,10] However, the significance of this complication of radiation therapy was not fully appreciated until 20 years later when Luxton and his colleagues[21,22] reported the development of renal insufficiency in 20 percent of patients exposed to in excess of 2300 rads over a period of less than 5 weeks. Subsequent to these early reports and despite efforts in radiation therapy to exclude the kidneys from the field of radiation, reports of alterations in renal function resulting from exposure continue to be a cause of concern. Moreover, it is often necessary to include the renal regions in the radiation field where metastasis, Wilms' tumor or periaortic disease is involved.[23] Further, a number of cases have been reported in which radiation nephritis has occurred when total exposure was well below what Luxton believed necessary to cause renal impairment.[28,33] These reports become especially important since renal irradiation continues to be a routine part of transplantation procedures[13] and whole-body irradiation is being employed as an adjunct in the treatment of leukemic disease.[32]

Radiation nephritis is characterized by an asymptomatic or latent period of 3-6 months, after which the individual shows the signs and symptoms of renal insufficiency. At present little information exists concerning alterations in renal function during this period. In fact, the only study in man where the acute effects of radiation were evaluated was done by Avioli and colleagues.[3] They reported that glomerular filtration rate (GFR), renal blood flow (RBF) and the tubular maximum for the secretion of p-aminohippuric acid (Tm_{PAH}) were suppressed within 24 hours after receiving

1

400 rads. However, 24 hours after patients received 500 rads or cumulative doses up to 1650 rads there was a transient rise in GFR. Renal function as evaluated by these parameters was depressed 75-80 percent in three patients 12 months after receiving cumulative doses of 2000 to 2400 rads.

As in man, the acute effects of ionizing radiation on renal function have not been well described in experimental animals. In 1953, Mendelsohn and Caceres[25] reported a gradual decline in GFR, RBF and Tm_{PAH} in a single uninephrectomized dog receiving 3680 rads over a 13-day period. At 10 months, only Tm_{PAH} had returned to near preirradiation levels. Similar studies carried out in another dog receiving 2700 rads showed an initial but transient rise in GFR and RBF followed by a decline in all parameters studied over a 2-month interval. By 7 months, RBF and Tm_{PAH} had returned to control values although GFR remained depressed. In both dogs, gross examination of the kidneys indicated large polar areas of normal and hypertrophic renal tissue while areas of fibrosis and scarring seemed limited to the central areas of the first dog and included only the lower pole in the second. In a preliminary communication, Klapproth and colleagues[19] reported that in two uninephrectomized dogs which had received local doses of 1800 and 3600 rads, in 600-rad increments, Tm_{PAH} fell sharply while plasma clearances of PAH and creatinine were only slightly depressed. They concluded that the initial site of injury was in the renal tubule. In support of this concept are the works of Maier and Casarett[24] who noted that when one or both kidneys of dogs were irradiated with single doses of 1000 to 2000 rads there was a transient rise in urine output associated with a concomitant fall in urinary specific gravity 2 to 3 weeks following exposure. Since these animals had normal levels of blood urea nitrogen, it

was assumed that GFR was normal. Further, Coburn et al.[4] reported that, in two uninephrectomized dogs locally irradiated with single doses of 2965 rads and one with 2685 rads, profound impairment of collecting-duct function occurred within 13 days of exposure while GFR did not decline until 28 days later.

In contrast to these observations, Záruba[36] reported only equivocal changes in GFR, RBF, and Tm_{PAH} within the first 28 days in groups of dogs where both kidneys were exposed to single doses of 400, 1600, and 2400 R.

It seems likely that the renal tubule is the initial site of injury. Defects in the function of the proximal tubule and the concentrating segment of the nephron have been described. It is difficult, however, to develop a concept of renal tubular injury following x irradiation, in the presence of the above-described conflicting information, especially since the results of those studies where positive effects were demonstrated are based on very small sample sizes at varying dose levels. Further, in the studies cited, it is not possible to eliminate the effects of renal hypertrophy, either in the unexposed areas of the irradiated kidney or in the contralateral kidney, nor is it possible to determine what effects are the result of changes in the environment resulting from the poorly functioning irradiated kidney or kidneys.

Utilizing the split-bladder model in the dog of the present study made it possible to eliminate the above-listed factors and to determine some of the acute intrinsic effects of ionizing radiation on renal function. This study indicated that in the dog, while GFR initially remained unchanged, there is a marked impairment in proximal tubular reabsorption of sodium within 24 hours and in collecting-duct function within 21 days after receiving single doses of 2000 rads.

3

II. METHODS

Sixteen healthy adult female beagle dogs weighing 8 to 12 kg were used in this study. They were fed standard dog chow with supplemental horsemeat. Ten to fourteen days before an animal was initiated into the study, urinary hemibladders were surgically formed according to the method described by Desautels[6] and Sturim et al.[31] This surgical procedure allowed for the separate collection of urine from each kidney through cystostomy tubes which had been sewn into each hemibladder and brought out through the lower abdominal wall. The dogs were divided into two groups and utilizing standard clearance techniques they were studied in an unanesthetized state under conditions of water diuresis (protocol I) and osmotic diuresis (protocol II).

Protocol I. These studies were performed in 10 dogs. All dogs were given 400 to 800 ml of water per intragastric tube, followed by an intravenous infusion of 0.45 percent NaCl at the rate of 2 to 4 ml/min. The amount of water given orally and the rate of infusion necessary to produce a state of water diuresis were determined for each animal during preirradiation observations. After the period of equilibration and while the animals were in a state of water diuresis, three timed urine collections were obtained. Upon completion of these collections, an infusion of vasopressin (Pitressin, Parke, Davis and Company) at 4 mU/min was begun. When urine output had fallen and a state of antidiuresis was produced, two more clearance periods were obtained.

Protocol II. Six dogs were studied using this protocol. Eighteen to twenty-four hours after all food and water were withheld, urine and blood were collected for the determination of osmolality. Upon the completion of these collections, a 15 percent

4

mannitol solution was infused at a rate of 5 ml/min. A priming dose of 100 mU of vasopressin was given and 1 mU/min was infused in the sustained solution. Three timed urine collections were obtained while the dogs were in a state of osmotic diuresis. Under these conditions the tubular maximum for the reabsorption of free water ($Tm^c_{H_2O}$) was calculated utilizing the formula $C_{osm} - V$ where C_{osm} is the osmolar clearance and V is the urine flow.

In both of these protocols, GFR and RBF were determined by measuring the clearance of inulin and PAH respectively. All dogs were infused with solutions containing appropriate amounts to maintain plasma inulin levels at 50-100 mg/100 ml and PAH levels at 0.5 - 2.0 mg/100 ml. After the priming doses were given, the dogs were allowed to equilibrate for at least 30 minutes. Blood was drawn at the midpoint of each timed urine collection through a catheter placed in a leg vein.

The left kidney of each dog received 2000 rads of x irradiation at the rate of 83.8 rads/min. The x-ray source was an x-ray generator (Maxitron 300, General Electric) with the following physical parameters: 300 kVp, 20 mA, 2.0 mm Be + 1.54 mm Cu filtration. The target to subject midline distance was 60 cm. The effective energy content of the x rays was 96 keV. With the exception of a 5 x 5-cm port over the left kidney, the dog was shielded with 1/4-inch lead. The position of the left kidney was determined by manual palpation and intravenous pyelography. Dosimetry was determined utilizing Shonka chambers in phantom dogs. These studies also indicated that the contralateral kidney was exposed to 9.4 percent of the total dose administered. Irradiation was performed while the dogs were under Nembutal anesthesia (20 mg/kg).

5

Clearance measurements were obtained from dogs in each protocol 1-2 days before irradiation and on day 1 and at 7-day intervals postirradiation. Of the 10 dogs studied under conditions of water diuresis, two were euthanatized following studies done on the 14th day and four were euthanatized after clearance measurements were obtained on the 28th day postexposure. The remaining four dogs were studied again 56 days after irradiation. All six dogs studied under conditions of osmotic diuresis were studied on day 1 and at weekly intervals for 28 days and again 56 days following irradiation. In most cases, kidney tissue was obtained for histological evaluation within 5 minutes after euthanasia.

In most studies the concentrations of inulin and PAH were measured by the methods of Heyrovsky[12] and Harvey and Brothers,[11] respectively, as modified for automated simultaneous determination by Sobocinski and Hibernik.[30] In five studies, inulin and PAH were measured by hand. In these studies, inulin concentrations were determined by the method of Davidson and Sackner.[5] Mean recoveries from these two methods were not different. Sodium and potassium were measured by internal standard flame photometry. Inorganic phosphorus was measured in plasma and urine by the method of Hurst,[15] as modified for the AutoAnalyzer by Kraml.[20] Urine and plasma osmolalities were determined with an Advanced osmometer.

All data were evaluated for statistical significance, utilizing the Student's "t" test for paired data. Data collected for each parameter were evaluated for significance after logarithmic transformation in those cases where the ratios of the irradiated to the control kidney at preirradiation times were compared to ratios at postirradiation intervals. The absolute and fractional excretion data tended to be more normally

distributed after logarithmic transformation and were therefore tested for significance in this state.

III. RESULTS

The mean weight of animals was the same in both groups, averaging 9.1 ± 1.7 kg (SD) in the first protocol and 9.9 ± 1.2 kg in the second protocol. In both groups there was a significant loss of weight within the first 2 weeks of the study. The mean weight loss over this period was 0.89 ± 0.14 kg in the first group and 0.91 ± 0.13 kg in the second group. After 28 days, weight loss was variable. Five of ten dogs became anorectic and lost nearly 40 percent of their body weight. Two of the anorectic dogs which were not euthanatized died within 2 weeks of the 56-day experiments. While all dogs with profound weight loss had significant renal impairment, based on measurements of GFR, there was no correlation between the severity of the weight loss and the degree of renal insufficiency.

Within 14 days of exposure, all dogs exhibited an eschar at the site of irradiation followed by permanent epilation. No other extrarenal effects of radiation were evident. At no time was there any evidence of gastrointestinal irritation. White blood cell counts and hematocrit determinations performed at weekly intervals on all dogs remained within the normal range.

With the exception of tissue obtained 56 days after exposure, all renal tissue examined grossly and with light microscopy (Figure 1) appeared normal for both control and irradiated kidneys. At 56 days there were marked differences on gross and microscopic inspection. The irradiated kidneys were highly variable in appearance, ranging from slightly smaller in size with minimal evidence of fibrosis and scarring

7

to marked diminution in size and striking fibrosis. In all six animals euthanatized at 56 days, the weight of the irradiated kidney was less than that of the control, averaging 27.8 and 39.8 g, respectively. Histological examination of the tissue revealed
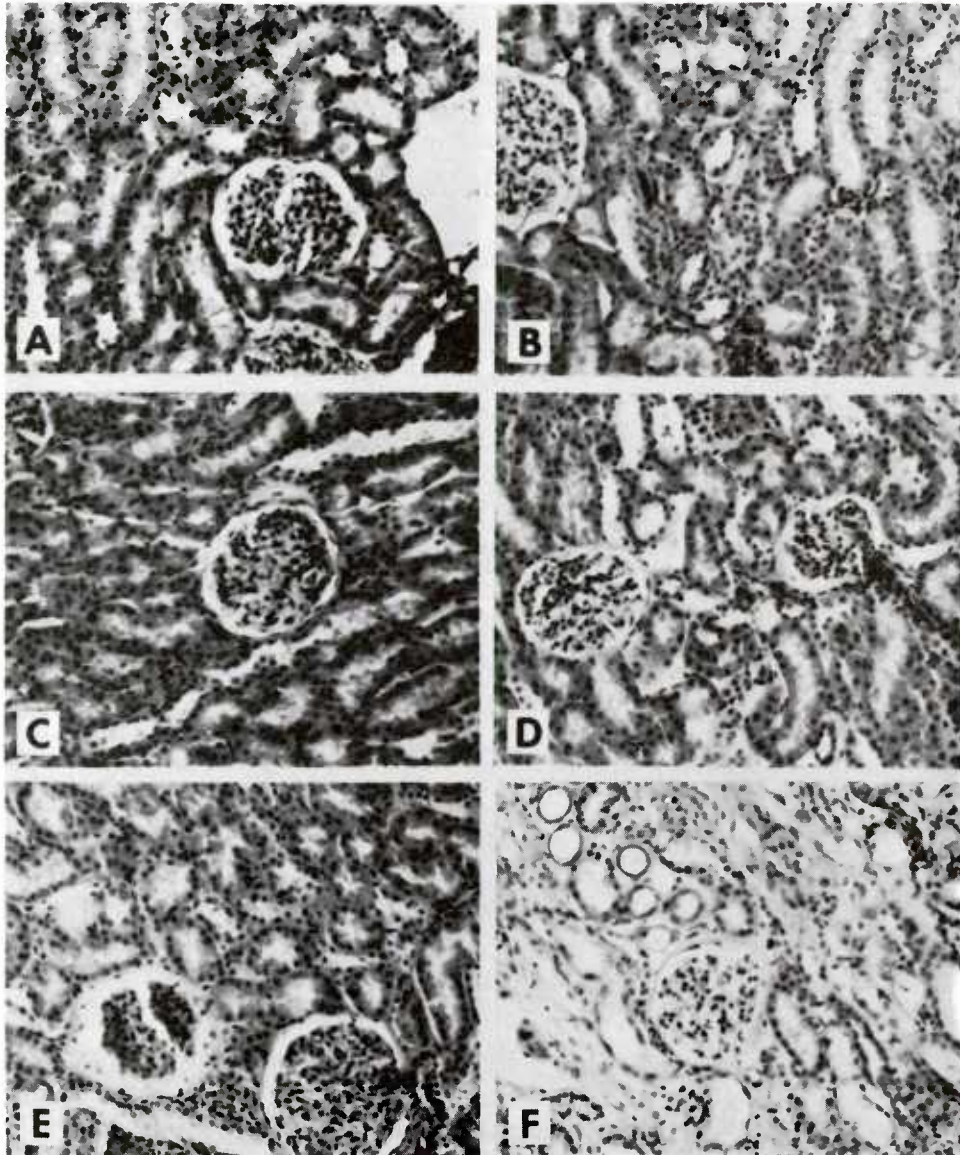

Figure 1. Photomicrographs of tissue obtained from the control and irradiated kidney of dogs euthanatized on days 14 (A, B), 28 (C, D) and 56 (E, F). There is little evidence of damage until day 56 when there is marked interstitial fibrosis and tubular destruction. Hematoxylin and eosin. X 100.

marked interstitial fibrosis with tubular dilatation and damage and only minimal damage to the glomeruli.

Protocol I. Water Diuresis. A summary of the clearance data collected while the animals were in a state of water diuresis is presented in Table I. The response to the water load and infusion of hypotonic saline was never as great after radiation exposure as before. Urine flow, free water clearance, and the absolute and fractional excretion of sodium were less following irradiation. These changes as well as the losses seen in body weight suggest that one effect of local irradiation is a reduction in the efficiency with which the animal is able to conserve water.

Although variable in the degree of response, the effects of radiation on renal function were apparent within 24 hours of exposure. During water diuresis, urine flow was significantly greater from the irradiated than from the control kidney at all of the intervals studied following exposure. Further, when the ratios of urine flow from the irradiated to the control kidney before irradiation were compared to mean ratios following exposure, there was a highly significant difference $(p < 0.001)$. When these ratios were plotted against time (Figure 2A), there was a significant positive correlation, indicating that the differences in urine flow became greater throughout the interval of the study $(r = 0.33, n = 59, p < 0.01)$. When the fractional excretion of water (V/GFR) is plotted in the same fashion (Figure 2B), the increasing disparity in the excretion of water is even more apparent $(r = 0.64, n = 59, p < 0.001)$.

The absolute and fractional excretions of sodium from the irradiated kidney were significantly greater 24 hours after exposure. When the ratios of the irradiated to the control kidney for the fractional excretion of sodium were plotted against time, it was

Table I. Water and Solute Excretion during Water Diuresis at a Preirradiation Time and at the Intervals Studied Postirradiation

Time	N	Kidney	V (ml/min)	GFR (ml/min)	C_{PAH} (ml/min)	U_{osm} (mosmol/liter)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}V$ (μeq/min)	U_KV (μeq/min)	U_PV (μM/min)	$\frac{V}{GFR}$ x 100 (percent)	$\frac{C_{H_2O}}{GFR}$ x 100 (percent)	$\frac{C_{Na}}{GFR}$ x 100 (percent)	$\frac{C_K}{GFR}$ x 100 (percent)	$\frac{C_P}{GFR}$ x 100 (percent)
Pre-Irradiation	10	CK	2.20 ± 0.36	28.2 ± 2.1	81.92 ± 5.6	121 ± 20.0	0.82 ± 0.13	1.41 ± 0.27	31.5 ± 11.9	11.7 ± 1.8	3.11 ± 0.42	8.00 ± 1.23	5.02 ± 0.83	0.92 ± 0.38	13.3 ± 2.1	10.3 ± 1.6
		IK	2.27 ± 0.36	28.7 ± 2.2	80.22 ± 5.8	123 ± 21.4	0.30 ± 0.12	1.49 ± 0.28	32.1 ± 11.8	11.3 ± 1.6	3.14 ± 0.44	8.22 ± 1.30	5.34 ± 0.92	0.92 ± 0.37	12.6 ± 2.0	10.2 ± 1.7
Post-Irradiation																
Day 1	10	CK	1.43 ± 0.23§	26.4 ± 1.4	77.9 ± 5.5	162 ± 36.0§	0.56 ± 0.06‡	0.88 ± 0.23‡	12.9 ± 3.4§	12.4 ± 1.4*	2.22 ± 0.56§	5.43 ± 0.69§	3.26 ± 0.82§	0.37 ± 0.11‡	14.1 ± 1.4	6.92 ± 1.11§
		IK	1.96 ± 0.31	28.0 ± 1.9	81.1 ± 5.4	124 ± 25.3	0.64 ± 0.09	1.34 ± 0.31	19.6 ± 5.6	14.9 ± 1.8	2.83 ± 0.71	6.91 ± 0.79	4.58 ± 0.90	0.54 ± 0.18	15.6 ± 1.1	8.83 ± 1.53
Day 7	10	CK	1.31 ± 0.21‡	28.9 ± 2.3	98.7 ± 6.6	152 ± 32.6*	0.54 ± 0.07	0.77 ± 0.22*	8.2 ± 1.6*	9.65 ± 1.4	4.02 ± 0.75	4.78 ± 0.80*	2.88 ± 0.77*	0.23 ± 0.05	10.2 ± 1.6‡	13.6 ± 2.9
		IK	1.82 ± 0.21	29.8 ± 2.2	98.5 ± 8.3	100 ± 12.0	0.57 ± 0.08	1.25 ± 0.18	11.2 ± 2.5	13.4 ± 2.3	3.63 ± 0.80	6.27 ± 0.72	4.29 ± 0.57	0.29 ± 0.08	14.4 ± 2.8	11.5 ± 2.7
Day 14	10	CK	1.12 ± 0.15‡	26.5 ± 1.5	91.0 ± 8.1	189 ± 31.3‡	0.55 ± 0.04	0.57 ± 0.15‡	12.43 ± 3.3*	9.10 ± 0.96*	3.59 ± 0.62	4.28 ± 0.54‡	2.17 ± 0.56§	0.33 ± 0.09*	9.94 ± 0.66	12.7 ± 2.5
		IK	1.71 ± 0.17	27.2 ± 1.7	90.8 ± 6.5	116 ± 10.2	0.59 ± 0.04	1.12 ± 0.16	18.09 ± 4.5	11.1 ± 1.70	3.29 ± 0.73	6.39 ± 0.53	4.16 ± 0.52	0.48 ± 0.12	11.7 ± 1.4	10.8 ± 2.0
Day 21	8	CK	1.55 ± 0.20‡	28.0 ± 1.7	98.74 ± 11.9	155 ± 25.2‡	0.77 ± 0.16	0.88 ± 0.22‡	15.8 ± 4.3*	13.0 ± 2.2	5.20 ± 1.1	5.69 ± 0.68‡	3.07 ± 0.68‡	0.44 ± 0.15‡	12.8 ± 1.9	16.1 ± 4.0
		IK	2.33 ± 0.27	28.2 ± 2.3	93.6 ± 10.2	95 ± 10.2	0.72 ± 0.11	1.61 ± 0.24	22.2 ± 5.3	13.4 ± 2.2	4.28 ± 0.87	8.40 ± 0.79	5.71 ± 0.61	0.61 ± 0.17	12.9 ± 1.8	13.1 ± 2.8
Day 28	8	CK	1.21 ± 0.13‡	27.4 ± 2.0	81.9 ± 9.8	346 ± 165§	0.66 ± 0.06	0.57 ± 0.17‡	9.96 ± 0.93§	11.2 ± 1.1	4.20 ± 0.78	4.17 ± 0.92‡	1.78 ± 0.90§	0.26 ± 0.03§	12.6 ± 2.4	13.5 ± 2.9
		IK	2.05 ± 0.17	28.7 ± 3.0	77.8 ± 9.0	154 ± 62.9	0.65 ± 0.05	1.44 ± 0.15	15.2 ± 1.8	11.3 ± 0.87	3.64 ± 0.66	7.91 ± 1.06	4.88 ± 0.70	0.40 ± 0.05	12.9 ± 2.7	11.1 ± 1.6
Day 56	4	CK	1.00 ± 0.21	27.5 ± 1.4	85.5 ± 10.3	239 ± 45.0*	0.60 ± 0.04	0.51 ± 0.22‡	14.2 ± 3.4	13.6 ± 1.9	2.78 ± 0.90	2.88 ± 0.11§	1.58 ± 0.89*	0.35 ± 0.08	18.5 ± 5.6	10.9 ± 3.7
		IK	1.66 ± 0.24	21.2 ± 2.4	66.34 ± 12.4	100 ± 6.0	0.52 ± 0.07	1.14 ± 0.18	17.5 ± 3.2	11.7 ± 3.2	2.01 ± 0.61	7.84 ± 0.65	5.34 ± 0.49	0.57 ± 0.06	20.6 ± 6.7	9.91 ± 2.65

N, number of dogs studied; CK, control kidney; IK, irradiated kidney; V, urine flow; GFR, glomerular filtration rate; C_{PAH}, clearance of p-aminohippuric acid; U_{osm}, urine osmolality; C_{osm}, osmolar clearance; C_{H_2O}, free water clearance; $U_{Na}V$, absolute rate of sodium excretion; U_KV, absolute rate of potassium excretion; U_PV, absolute rate of inorganic phosphorus excretion; V/GFR x 100, fractional excretion of water; C_{H_2O}/GFR x 100, free water clearance factored by GFR; C_{Na}/GFR x 100, fractional excretion of sodium; C_K/GFR x 100, fractional excretion of potassium; C_P/GFR x 100, fractional excretion of inorganic phosphorus. Values are the mean ±SE.

* Control versus irradiated kidney $P < 0.05$
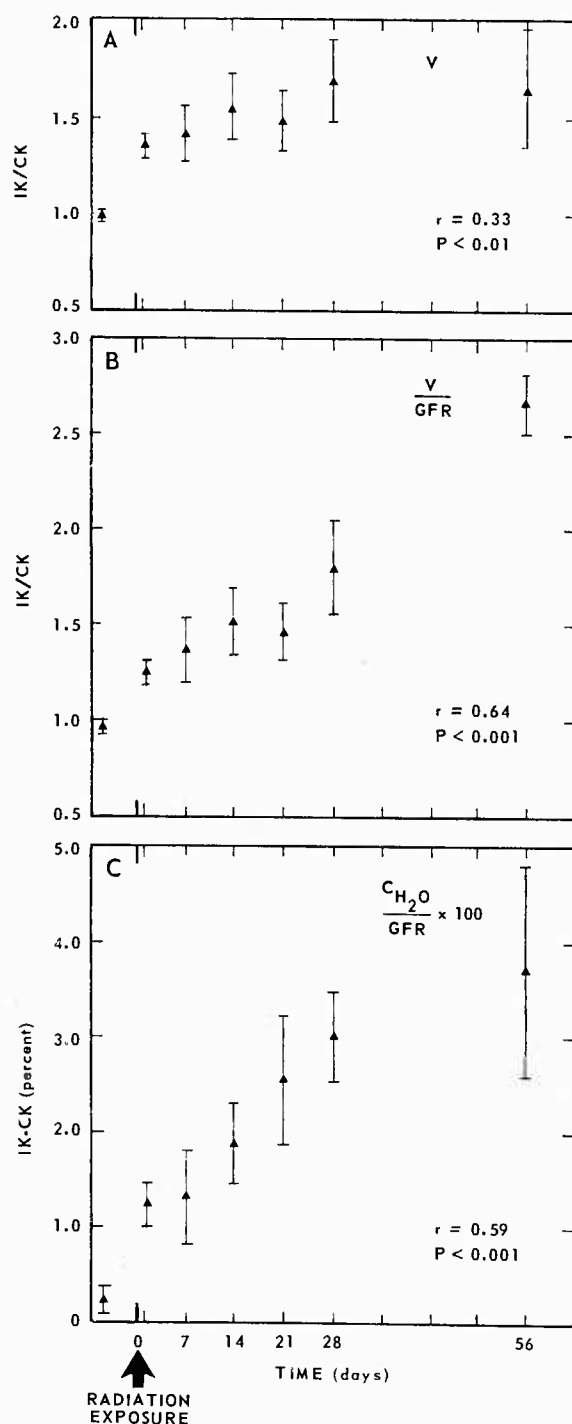† $P < 0.01$
‡ $P < 0.005$
§ $P < 0.001$

Figure 2. Water excretion during water diuresis. The mean and standard errors for the ratios of the irradiated kidney to the control kidney (IK/CK) for urine flow (V) and the fractional excretion of water (V/GFR) are plotted against time in panels A and B, respectively. In panel C, the difference (IK–CK) in the percent of free water excreted factored by GFR (C_{H_2O}/GFR x 100) is plotted in a similar fashion.

11

apparent that differences in sodium excretion appear to persist throughout the interval

of the study (Figure 3A). This was not the case for the excretion of phosphate, potas-

sium or total solute. Phosphate excretion rose significantly within 24 hours but

returned to nearly control levels by the 7th day postexposure. Differences in the

absolute and fractional excretion of potassium tended to lag behind that of sodium and

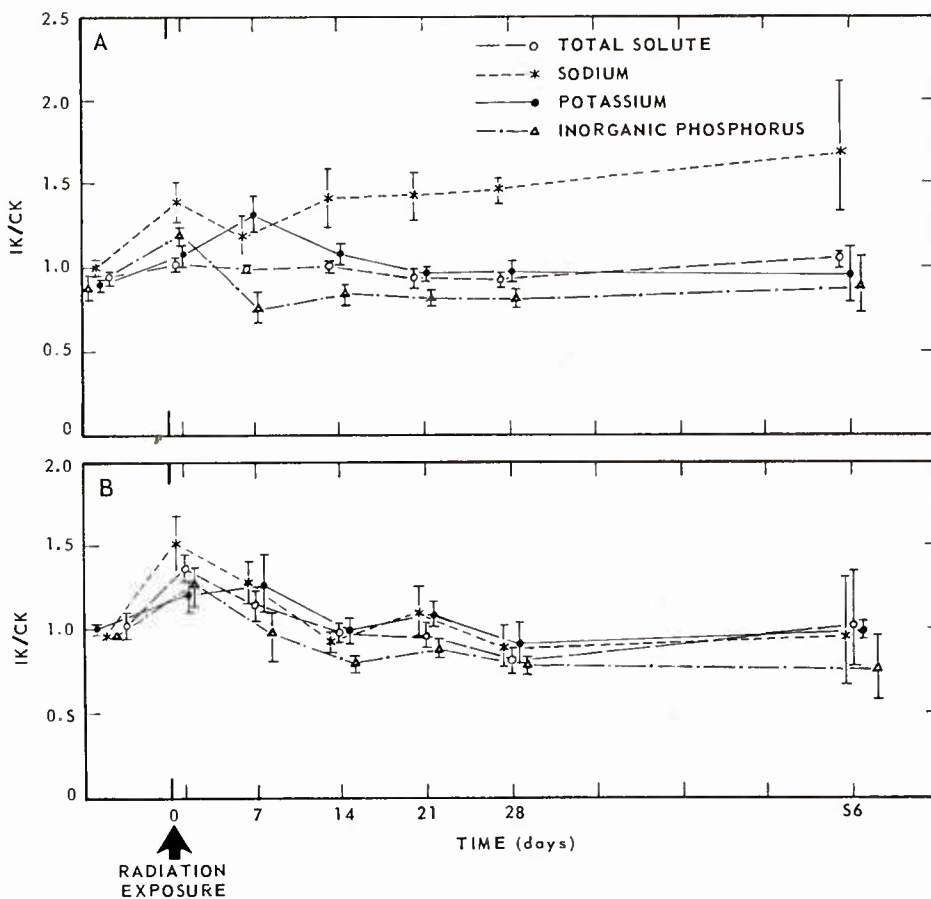phosphate but were significantly greater by day 7 and again were not different from

Figure 3. Solute excretion in water diuresis and antidiuresis.
The mean and standard errors of the ratios of the
irradiated to the control kidney (IK/CK) for the frac-
tional excretion of total solute, sodium, potassium
and inorganic phosphorus in water diuresis (A) and
in antidiuresis (B) are plotted against time.

12

control values by day 14. Despite these highly significant increases in the excretion of these ions, the excretion of solute at all of the intervals of the study was unchanged. It was therefore not surprising to find that differences in urine flow seen between the two kidneys were highly correlated to differences in the excretion of free water (Figure 4B) but not at all to changes in osmolar clearance (C_{osm}) (Figure 4A). Further, when the differences between the irradiated and the control kidney for C_{H_2O} factored by GFR are plotted against time, it is apparent that these differences became greater with time ($r = 0.59$, $n = 59$, $p < 0.001$) (Figure 2C) and tend to parallel changes in the absolute and fractional excretion of water (Figure 2A, B).

During the first 28 days following exposure to radiation, the GFR of the irradiated kidney was never significantly different from the control kidney. By day 56, however, the GFR of the exposed kidney was reduced in three of four dogs while unchanged in the other. Similarly, renal blood flow to the irradiated kidney remained stable for the first 28 days but had declined in the same three dogs 56 days following exposure.

Antidiuresis. The effect of vasopressin can be seen by comparing data collected during water diuresis and summarized in Table I and data collected after the infusion of vasopressin was begun which is presented in Table II.

Vasopressin produced a marked reduction in urine flow within 20 minutes after the infusion in all of the dogs at all of the intervals of the study. This reduction was highly significant ($p < 0.005$) at all of the times studied, with the exception of the 56-day collections. On that day, partially because of the small sample size and because control collections from one dog were low before the onset of antidiuresis,
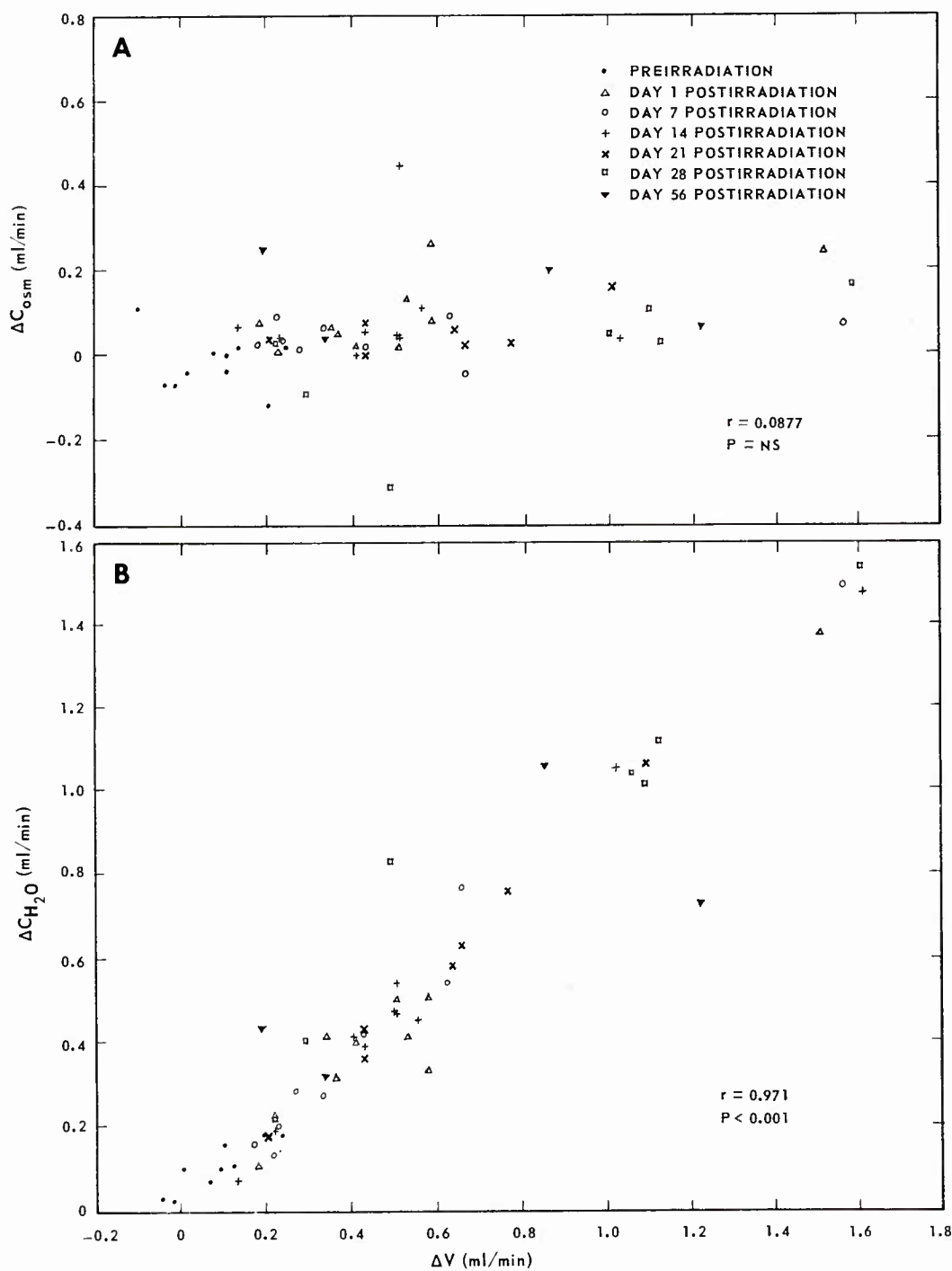
13

Figure 4. Relations between the differences of the irradiated and control kidney in the osmolar clearance (ΔC_{osm}, A) and free water clearance (ΔC_{H_2O}, B) and the differences in urine flow (ΔV) in water diuresis are shown at a preirradiation time and on days 1, 7, 14, 21, 28 and 56 postirradiation.

Table II. Water and Solute Excretion after the Administration of Vasopressin to Hydrated Dogs at a Preirradia-tion Time and at the Intervals Studied Postirradiation

Time	N	Kidney	V (ml/min)	GFR (ml/min)	C_{PAH} (ml/min)	U_{osm} (mosmol/liter)	C_{osm} (ml/min)	$T^c_{H_2O}$ (ml/min)	$U_{Na}V$ (μeq/min)	$U_K V$ (μeq/min)	$U_P V$ (uM/min)	$\frac{V}{GFR}$ x 100 (percent)	$\frac{T^c_{H_2O}}{GFR}$ x 100 (percent)	$\frac{C_{Na}}{GFR}$ x 100 (percent)	$\frac{C_K}{GFR}$ x 100 (percent)	$\frac{C_P}{GFR}$ x 100 (percent)
Pre-Irradiation	10	CK	0.51 ± 0.11	33.4 ± 3.4	82.9 ± 7.4	825 ± 106	1.18 ± 0.17	0.69 ± 0.06	82.2 ± 19.0	15.8 ± 3.0	3.59 ± 0.70	1.89 ± 0.58	2.31 ± 0.40	2.83 ± 0.83	16.8 ± 4.6	10.9 ± 2.3
		IK	0.49 ± 0.11	32.6 ± 3.1	83.3 ± 7.3	833 ± 112	1.14 ± 0.17	0.65 ± 0.06	76.5 ± 16.0	15.1 ± 2.5	3.68 ± 0.70	1.86 ± 0.55	2.29 ± 0.36	2.71 ± 0.74	17.1 ± 4.4	11.0 ± 2.1
Post-Irradiation																
Day 1	10	CK	0.36 ± 0.08§	27.2 ± 2.0†	72.0 ± 5.2	902 ± 129*	0.89 ± 0.14§	0.52 ± 0.07§	67.9 ± 15.0	16.8 ± 4.1*	2.86 ± 0.61‡	1.35 ± 0.30‡	1.91 ± 0.22§	2.35 ± 0.65‡	23.6 ± 7.4*	10.0 ± 2.2†
		IK	0.54 ± 0.10	30.3 ± 2.4	82.2 ± 3.9	770 ± 92.9	1.21 ± 0.19	0.68 ± 0.10	105.0 ± 21.5	22.3 ± 4.4	3.94 ± 0.84	1.98 ± 0.44	2.41 ± 0.30	3.27 ± 0.70	29.4 ± 8.1	13.5 ± 3.0
Day 7	10	CK	0.44 ± 0.11	26.6 ± 1.9	81.8 ± 8.2	894 ± 182	0.92 ± 0.15*	0.50 ± 0.09	73.1 ± 16.2	14.8 ± 3.5*	4.36 ± 0.67	1.73 ± 0.46*	1.90 ± 0.35	2.09 ± 0.54*	17.2 ± 4.4*	16.0 ± 2.8
		IK	0.56 ± 0.12	26.6 ± 2.5	80.1 ± 4.2	719 ± 105	1.06 ± 0.18	0.50 ± 0.09	96.9 ± 20.6	18.23 ± 3.5	4.34 ± 0.64	2.29 ± 0.59	1.80 ± 0.40	2.81 ± 0.69	22.2 ± 5.2	15.4 ± 2.4
Day 14	10	CK	0.42 ± 0.09	29.8 ± 2.3	82.5 ± 5.9	760 ± 65.3	0.99 ± 0.16	0.57 ± 0.08	81.6 ± 18.0	13.2 ± 1.8	4.42 ± 0.77	1.50 ± 0.31	1.98 ± 0.27	2.14 ± 0.47	14.0 ± 2.1	13.9 ± 2.3
		IK	0.42 ± 0.10	27.2 ± 1.7	79.6 ± 5.3	763 ± 81.7	0.93 ± 0.15	0.51 ± 0.05	74.1 ± 17.7	12.5 ± 1.7	3.40 ± 0.55	1.65 ± 0.40	1.96 ± 0.21	2.12 ± 0.51	14.6 ± 2.2	11.7 ± 1.6
Day 21	8	CK	0.34 ± 0.10	24.3 ± 2.0	64.4 ± 4.5	835 ± 106	0.80 ± 0.17	0.49 ± 0.09	65.1 ± 19.1	9.86 ± 1.7	3.63 ± 0.57	1.41 ± 0.45	2.00 ± 0.35	1.90 ± 0.61	12.3 ± 2.2	13.2 ± 2.6
		IK	0.37 ± 0.10	23.4 ± 2.1	59.9 ± 4.6	704 ± 30.1	0.79 ± 0.18	0.42 ± 0.10	64.0 ± 18.5	10.5 ± 1.7	3.31 ± 0.65	1.64 ± 0.45	1.79 ± 0.38	2.00 ± 0.59	14.0 ± 2.2	12.5 ± 2.6
Day 28	8	CK	0.39 ± 0.11	25.4 ± 1.9	67.9 ± 6.0	849 ± 115	0.91 ± 0.17	0.52 ± 0.08†	70.8 ± 20.2	12.4 ± 1.9	3.21 ± 0.71	1.68 ± 0.51	2.12 ± 0.38†	2.19 ± 0.70	15.6 ± 2.7	12.1 ± 2.9
		IK	0.50 ± 0.12	27.8 ± 5.0	64.0 ± 10.9	581 ± 110	0.79 ± 0.17	0.30 ± 0.08	65.6 ± 19.9	12.5 ± 2.1	2.86 ± 0.60	2.07 ± 0.58	1.43 ± 0.35	2.14 ± 0.70	16.1 ± 3.4	11.0 ± 3.0
Day 56	4	CK	0.49 ± 0.07	27.4 ± 2.9	71.7 ± 9.8*	538 ± 48.3	0.73 ± 0.11	0.30 ± 0.12	66.7 ± 16.2	15.1 ± 3.5	2.71 ± 0.45	1.88 ± 0.37	1.47 ± 0.41	1.94 ± 0.54	14.2 ± 2.1	14.5 ± 4.4
		IK	0.45 ± 0.06	24.5 ± 3.0	58.1 ± 8.2	488 ± 85.7	0.79 ± 0.17	0.37 ± 0.11	72.5 ± 24.3	14.2 ± 4.4	2.95 ± 0.83	2.18 ± 0.59	1.64 ± 0.57	2.63 ± 1.07	15.5 ± 3.4	12.7 ± 4.6

$T^c_{H_2O}$, negative free water clearance; $T^c_{H_2O}$/GFR, negative free water clearance factored by GFR. See Table I for remaining abbreviations and footnotes.

differences in urine flow following vasopressin were significant only at the 5 percent level from the irradiated kidney and not at all from the control kidney. As expected, the decline in urine flow was associated with a highly significant ($p < 0.001$) increase in urinary osmolality. Again, changes in urinary osmolality were associated with lower levels of significance at 56 days. Total solute and sodium excretion were also significantly elevated in antidiuresis.

While GFR did not seem remarkably affected by the administration of the antidiuretic hormone, the renal blood flow to the irradiated kidney was significantly reduced in antidiuresis 7, 14 and 21 days after irradiation. These changes were not consistently seen in all dogs but did achieve significance at the 5 percent level of probability. The RBF to the control kidney tended to be lower in antidiuresis but this decrease was not statistically significant.

Despite the changes in RBF seen in the irradiated kidney in response to the administration of vasopressin, there were no significant differences seen between control and irradiated kidneys until day 56. At this time there was a mean reduction of 18.6 percent (range 3-30 percent) in the renal blood flow to the irradiated kidney.

There was a transient but significant rise in GFR of the irradiated kidney of nearly 16 percent on the 1st day following exposure. After which, GFR was nearly the same for both kidneys until day 56 when there was a mean reduction in the GFR of the irradiated kidney of 10.7 percent (range 3-40 percent).

Although urine flow from the irradiated kidney was reduced in response to vasopressin, there were highly significant differences 24 hours after irradiation. Urine flow from the irradiated kidney was nearly 65 percent greater than from the control

kidney. This initial increase was only partially the result of changes in GFR since the differences seen between the two kidneys were only slightly reduced when urine flow was factored by GFR.

As was seen during water diuresis, the absolute and fractional excretions of sodium, potassium and inorganic phosphorus during antidiuresis were greater from the irradiated kidney within 24 hours after irradiation, with differences in potassium excretion tending to lag behind. Surprisingly, when the ratios of these ions are plotted against time, all, including sodium excretion, were not different from control values by day 14 (Figure 3B). The early changes seen in the excretion of these ions were accompanied by a significant difference in the excretion of total solute which, unlike changes seen in water diuresis, was closely correlated with the early changes in urine flow (Figure 5A). The differences in osmolar clearance were well correlated to sodium excretion (Figure 5B). Further, negative free water clearance $(T^c_{H_2O})$ was actually greater at this time, averaging 0.52 ± 0.07 ml/min (SE) and 0.68 ± 0.10 ml/min ($p < 0.001$) from the control and irradiated kidneys, respectively, suggesting that differences seen initially in urine flow were not the result of a defect in the concentrating segment of the nephron.

When ratios of the irradiated kidney to the control kidney are plotted versus time for urine flow or the fractional excretion of water (Figure 6A, B), the differences tend to assume a biphasic curve. The excretion of water tended to be greater at two intervals. As previously described, urine flow was increased within 1 day of radiation exposure. This seemed to be related to the increase in the excretion of solute. Beginning about day 21, differences in the absolute and fractional excretion of water appeared
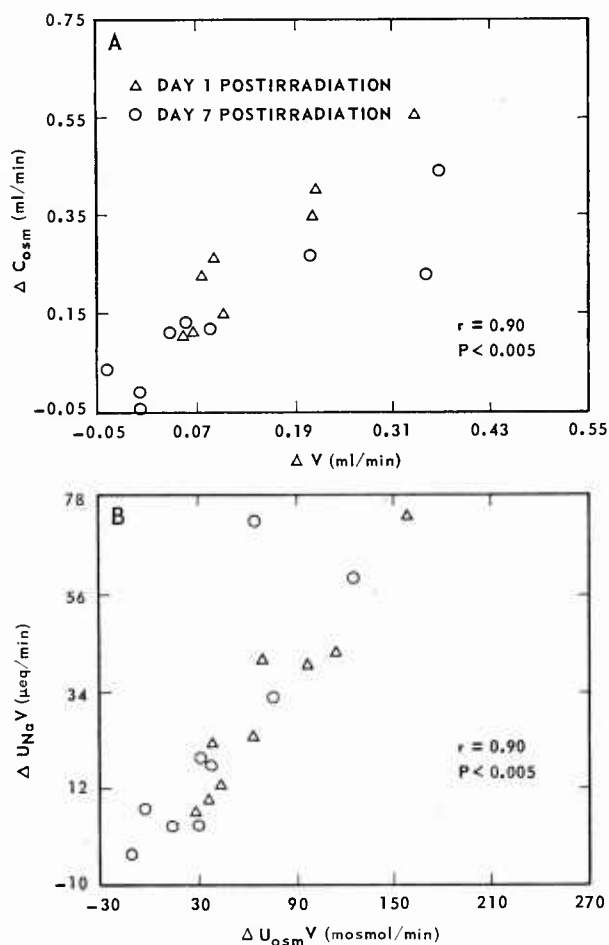
17

Figure 5.

Relations between differences in osmolar
clearance (ΔC_{osm}) and urine flow (ΔV)
and between differences in the excretion of
sodium ($\Delta U_{Na}V$) and total solute ($\Delta U_{osm}V$)
on days 1 and 7 in antidiuresis are shown
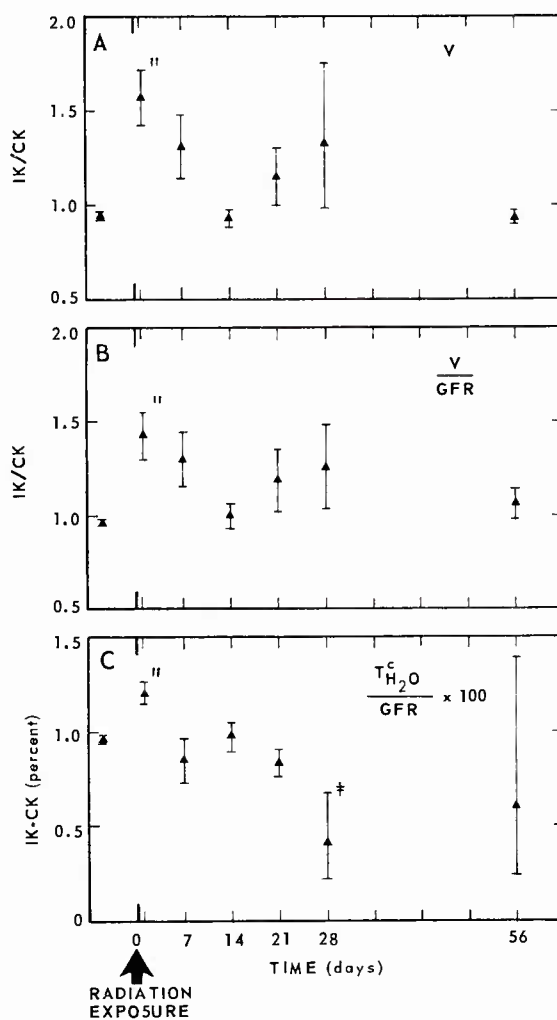in panels A and B, respectively.

Figure 6.

Water excretion during antidiuresis.
The mean and standard errors for the
ratios of the irradiated kidney to the
control kidney (IK/CK) for urine flow
(V) and the fractional excretion of
water (V/GFR) are plotted against
time in panels A and B, respectively.
In panel C, the difference (IK-CK) in
the percent of free water reabsorbed
factored by GFR ($T_{H_2O}^c$/GFR x 100)
is plotted in a similar fashion.
‡ $P < 0.01$, " $p < 0.001$, when the
ratios or differences are compared
to preirradiation values.

18

which were not significant but the high degree of variability suggested some abnormality in the reabsorption of water by the renal tubule. While no real differences in solute excretion were apparent at this time, differences in $T^c_{H_2O}$ (Figure 6C) were highly variable (range 0.019 - 0.286) and by day 28 there was a significant decrease in $T^c_{H_2O}$ from the irradiated kidney, averaging 0.52 ± 0.08 ml/min from the control and 0.30 ± 0.08 ml/min (p < 0.01) from the irradiated side. This suggested that the concentrating segment of the nephron was now impaired.

In an attempt to define more clearly this defect in the function of the concentrating segment, the second protocol was designed.

Protocol II. Table III summarizes the essential clearance measurements obtained from six dogs under the conditions of osmotic diuresis, as well as maximal urinary osmolalities obtained after food and water had been withheld 18-24 hours.

Table III. Total Solute and Water Excretion during Osmotic Diuresis at a Preirradiation Time and at the Intervals Studied Postirradiation

Time	Kidney	V (ml/min)	GFR (ml/min)	C_{PAH} (ml/min)	C_{osm} (ml/min)	$Tm^c_{H_2O}$ (ml/min)	$\frac{V}{GFR}$ x 100 (percent)	$\frac{Tm^c_{H_2O}}{GFR}$ x 100 (percent)	U_{osm}Max (mosmol/liter)	V_o (ml/min)
Pre-irradiation	CK	6.72 ± 0.92	26.1 ± 3.2	99.3 ± 9.9	7.79 ± 0.88	1.07 ± 0.09	26.3 ± 2.7	4.63 ± 0.89	1649 ± 166	0.024 ± 0.003
	IK	6.65 ± 0.89	26.9 ± 3.2	101 ± 8.6	7.74 ± 0.85	1.09 ± 0.09	25.5 ± 2.9	4.53 ± 0.85	1699 ± 140	0.021 ± 0.004
Post-irradiation										
Day 1	CK	5.74 ± 0.47[†]	25.1 ± 5.4[§]	85.8 ± 11.5[§]	6.67 ± 0.45	0.93 ± 0.07	26.3 ± 3.5	4.57 ± 0.92	1832 ± 122	0.022 ± 0.003
	IK	6.57 ± 0.41	28.0 ± 5.2	100 ± 13.6	7.56 ± 0.41	0.98 ± 0.09	26.6 ± 3.7	4.03 ± 0.70	1836 ± 147	0.026 ± 0.003
Day 7	CK	5.74 ± 0.59	22.7 ± 3.2	71.4 ± 5.7	6.71 ± 0.59	0.97 ± 0.12	26.5 ± 2.9	4.47 ± 0.59	1817 ± 157	0.021 ± 0.003
	IK	5.96 ± 0.46	23.8 ± 2.9	75.9 ± 5.6	6.97 ± 0.47	1.00 ± 0.09	26.2 ± 2.6	4.39 ± 0.42	1780 ± 154	0.023 ± 0.004
Day 14	CK	5.85 ± 0.57	21.1 ± 2.3	79.8 ± 9.5	6.64 ± 0.52	0.78 ± 0.13	28.5 ± 2.3	3.96 ± 0.69	1600 ± 100	0.020 ± 0.004
	IK	6.13 ± 0.56	22.9 ± 2.1	85.2 ± 8.8	6.93 ± 0.43	0.80 ± 0.15	27.8 ± 3.0	3.65 ± 0.62	1636 ± 130	0.024 ± 0.005
Day 21	CK	4.77 ± 0.34	21.5 ± 2.7	79.5 ± 9.2	5.74 ± 0.25	0.97 ± 0.14[+]	23.6 ± 2.8	4.72 ± 0.92[*]	1868 ± 104	0.027 ± 0.005
	IK	5.36 ± 0.49	22.6 ± 2.4	85.0 ± 10.0	5.87 ± 0.31	0.51 ± 0.24	25.3 ± 3.7	2.22 ± 1.17	1403 ± 148	0.034 ± 0.003
Day 28	CK	3.92 ± 0.34[‡]	20.9 ± 2.9	67.6 ± 9.4	5.10 ± 0.39	1.18 ± 0.10[§]	19.6 ± 1.0[+]	6.08 ± 0.72[‡]	1898 ± 259[*]	0.022 ± 0.003[*]
	IK	5.51 ± 0.18	22.6 ± 2.5	67.8 ± 6.2	5.53 ± 0.24	0.015 ± 0.13	25.9 ± 2.5	0.05 ± 0.58	930 ± 148	0.095 ± 0.051
Day 56	CK	5.84 ± 0.47[§]	27.2 ± 3.5[+]	90.9 ± 8.8[*]	6.72 ± 0.58	0.89 ± 0.16[*]	22.6 ± 1.0	3.33 ± 0.54[*]	1407 ± 167	0.059 ± 0.018
	IK	3.00 ± 0.69	13.9 ± 3.4	43.2 ± 8.4	3.09 ± 0.65	0.095 ± 0.06	23.4 ± 1.61	1.28 ± 0.61	978 ± 106	0.034 ± 0.006

$Tm^c_{H_2O}$, tubular maximum for the clearance of negative free water; $Tm^c_{H_2O}$/GFR, tubular maximum for the clearance of negative free water factored by GFR; U_{osm}Max, urine osmolality after 18-24 hours of complete water deprivation; V_o, urine flow after 18-24 hours of complete water deprivation. See Table I for remaining abbreviations and footnotes.

As was the case under conditions of antidiuresis, there was a transient highly significant increase in the GFR of the irradiated kidney on day 1 postexposure; after which, values were not different from control measurements until day 56. At that time there was a marked decline in the GFR of the irradiated kidney. Unlike the previous protocol, renal blood flow to the irradiated kidney was greater than to the control kidney within a day following exposure and tended to remain significantly greater through the 14th day. As was seen in protocol I, RBF to the irradiated kidney was significantly reduced by day 56.

When the ratios of the irradiated to the control kidney are plotted against time (Figure 7A), it is evident that differences in urine flow occurred at three different intervals. Within 24 hours after exposure, urine flow from the irradiated kidney was nearly 11 percent greater than from the control kidney. These differences seemed related to transient rises in GFR since the fractional excretion of water was the same for the irradiated and control kidneys.

Urine flow was significantly greater from the irradiated kidney 28 days after exposure. Further, when the ratios for the V/GFR are plotted against time (Figure 7B), it is evident that differences in the fractional excretion of water began to appear 21 days postexposure.

When similar ratios are plotted for the tubular maximum for the clearance of negative free water ($Tm_{H_2O}^c$) (Figure 7C), the increases in the absolute and fractional excretions of water seen 21 and 28 days after radiation exposure are associated with a marked decrease in $Tm_{H_2O}^c$, averaging 1.18 ± 0.10 ml/min from the CK and 0.015 ± 0.13 ml/min from the IK ($p < 0.001$). In fact, of the six dogs studied under these conditions,
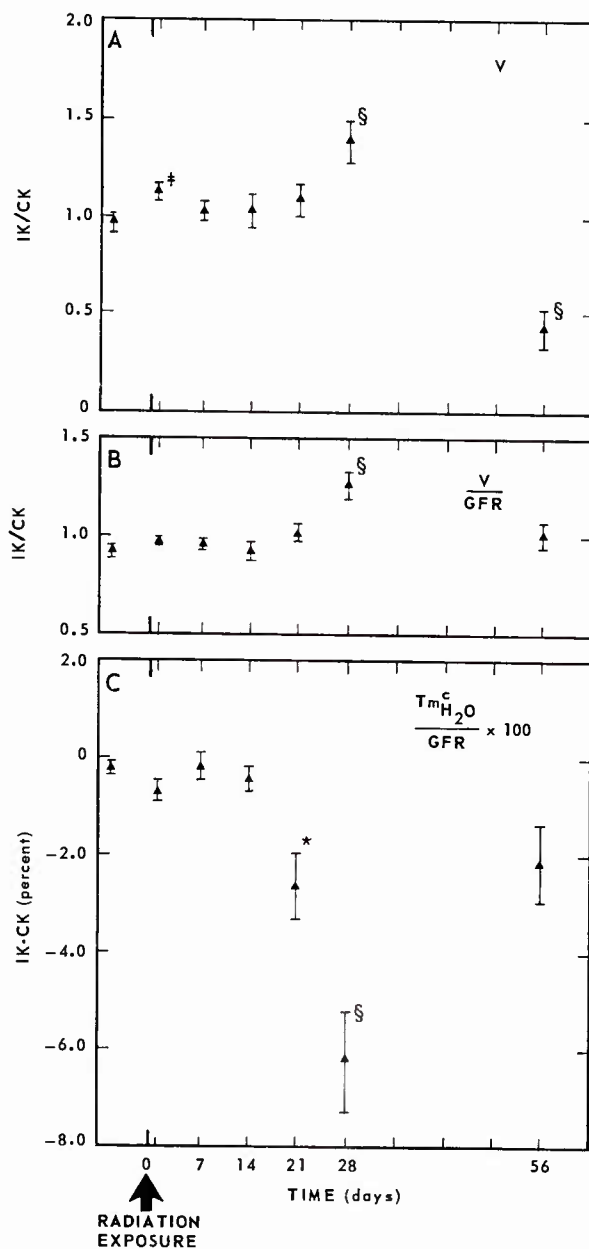
Figure 7. Water excretion during osmotic diuresis. The mean and standard errors for the ratios of the irradiated kidney to the control kidney (IK/CK) for urine flow (V) and the fractional excretion of water (V/GFR) are plotted against time in panels A and B, respectively. In panel C, the difference between the irradiated and control kidney (IK-CK) in the tubular maximum for the reabsorption of free water factored by GFR ($Tm^c_{H2O}/GFR \times 100$) is plotted against time. $*P < 0.05$, $\ddagger p < 0.01$, $\S p < 0.005$, when the ratios or differences are compared to preirradiation values.

21

four actually excreted free water. Similarly, the maximal concentrating ability of the irradiated kidney in response to water deprivation was diminished in all dogs by day 21 and, by day 28, the osmolality of urine collected from the irradiated kidney (930 ± 148 mosmol/liter) was almost half that of the control kidney (1898 ± 259 mosmol/liter, $p < 0.05$). This decline in urinary osmolality was associated with a concomitant and significant increase in urine flow from the irradiated kidney.

Finally, by day 56, urine flow was significantly less from the irradiated kidney, reflecting the reduction in GFR since fractional excretion of water from the two kidneys was not different.

IV. DISCUSSION

The present study demonstrates that there are marked disturbances in renal tubular function during the time when changes in GFR and RBF are small. These abnormalities consistently occurred in all dogs studied but were quite variable in severity from animal to animal.

The most obvious radiation effect on renal function was increased excretion of water. This effect was seen within 24 hours of exposure and was present throughout the interval of the study. On day 1, urine flow from the irradiated kidney was 40 percent greater than from the control kidney. Increased urine production has been reported in man[1, 16, 26, 27] and rats[7, 29] within 24 hours after total body exposure. Information collected from human exposure is fragmentary, with no evidence indicating that these changes are the result of intrinsic renal damage. The postirradiation diuresis in rats has been shown to occur when the renal masses only were exposed to radiation.[17, 18] Postirradiation diuresis in rats can be abolished by the administration

22

of pharmacologic doses of vasopressin[34,35] as well as water deprivation.[35] However, little information is available concerning the actual character of the diuresis or sites of injury in the nephron. In our studies it is apparent that under conditions of moderate hydration, differences in urine flow are primarily the result of increases in production and excretion of free water.

Free water is believed to be principally generated by the ascending limb of the loop of Henle and early distal tubule.[8] The amount of free water produced by this so-called diluting segment of the nephron is said to depend on the ability of the cells to extrude sodium actively without water into the interstitium and upon the amount of sodium present in the tubular lumen. Therefore, in the absence of changes in GFR, differences in free water production reflect differences in the ability of the proximal tubule to reabsorb sodium. These studies thus strongly suggest that, during water diuresis, differences in urine flow seen after irradiation are the result of injury to the proximal tubule which gives rise to a decrease in the reabsorption of sodium.

Surprisingly, radiation does not affect all transport systems in proximal tubules to the same degree. While the ability of the proximal tubule to reabsorb sodium is impaired almost immediately and seems to become worse throughout the study, as evidenced by continuing differences in the absolute and fractional excretion of sodium as well as the increasing differences in the excretion of free water, phosphate reabsorption is affected only initially. By day 7 postirradiation the absolute and fractional excretion of phosphate is not different from the contralateral control kidney during both water and antidiuretic states. Also, transiently, potassium excretion is greater. However, it is not clear from our studies whether the increases in excretion reflect

true damage to the transport mechanisms for potassium or whether the changes seen are more a reflection of a humoral response to water and sodium depletion; that is, increased aldosterone production.

The differences in urine flow seen on days 1 and 7 in the antidiuretic state resulting from the infusion of pharmacologic doses of vasopressin are difficult to explain. It is obvious that an osmotic diuresis is in progress, resulting most likely from the increased excretion of sodium. It is known that vasopressin gives rise acutely[2, 14] to a natriuresis which did occur in these animals. It is not clear how this is mediated. This study simply states that whatever mechanism is involved must be transiently enhanced by ionizing radiation.

At least initially there is no evidence that any other part of the renal tubule is affected. Data presented from the studies during water diuresis show marked increases in excretion of free water which indicate that the diluting segment of the nephron was not impaired during the initial 28 days postexposure.

Although the concentrating segment was functionally intact for at least 14 days after irradiation, there was definite evidence of marked impairment of function by day 21. When vasopressin was infused while the animals were in a state of mild water diuresis, $T^c_{H_2O}$ by the irradiated kidney tended to parallel the differences seen in urine flow. That is, at higher flows seen on day 1, reabsorption of free water by the concentrating segment was higher than control values and, as differences in urine flow disappeared over the next 2 weeks, $T^c_{H_2O}$ by the irradiated kidney approached control values. By day 21, however, there was marked impairment in the concentrating ability and by day 28, $T^c_{H_2O}$ was reduced by nearly half. In the second series of the studies

24

(protocol II), impairment in collecting–duct function is unequivocally shown. First, maximal urine osmolalities of the irradiated kidney, while initially not different, were all less than those obtained from the normally functioning kidney by day 21 and were reduced to 57 percent of control values by day 28. Similar results were obtained when the maximum for $T^c_{H_2O}$ was determined. These studies showed that, until 21 days after irradiation, $Tm^c_{H_2O}$ was the same for both kidneys, after which there was a striking reduction in the $T^c_{H_2O}$ maximum by the irradiated kidney. Further, these studies strongly support the suggestion that the increases in $T^c_{H_2O}$ seen 24 hours after exposure in protocol I but not in protocol II are the result of increases in the delivery of water to the concentrating segment rather than any real intrinsic change in function, since changes in the handling of sodium by the proximal tubule were not seen in protocol II as a result of the profound suppression in sodium reabsorption produced by the mannitol infusion.

The changes in collecting–duct function are present even after the decline in GFR and appear permanent. These observations agree well with information presented in the literature. The onset of the defects in reabsorption of free water coincides with the increases in urine output and fall in specific gravity noted by Maier and Casarett[24] after local doses of 1500 to 2000 rads. The fact that these changes appear earlier in the studies of Coburn et al.[4] suggests that the severity of the process might well be dose related since their dogs absorbed over 2500 rads.

The present experiments show an early transient rise in GFR and RBF within 24 hours of irradiation. These changes although small were highly significant in the antidiuretic phase of protocol I and in protocol II. A number of investigators,[3,19,25]

25

who have seen similar GFR and RBF damages, have postulated that these differences are the result of transient hyperemia; however, it is not clear what underlying mechanisms are involved. By 7 days, GFR and RBF had returned to near control values where they tended to remain for 4-6 weeks.

It is concluded that the most profound early effects of radiation on renal function, as demonstrated by the results of the present study, relate to the reduced conservation of sodium and water. This defect provides a possible explanation for the intitial weight loss seen in dogs in these studies as well as the diminished response to a water load seen following irradiation. The earliest change is a marked impairment in the handling of sodium by the proximal tubule followed in 3-4 weeks by a defect in the concentrating segment of the nephron. Changes in GFR and RBF are small initially and tend not to be severe until much later.

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13. ABSTRACT

Clearance studies were performed in 16 dogs with surgically formed hemibladders to evaluate the intrinsic renal effects of 2000 rads of x rays administered as a single dose to the left kidney. These studies were conducted under conditions of water diuresis in 10 dogs on days 1, 7 and 14 postexposure. Additional studies were performed 21 and 28 days after exposure in eight of these dogs and 56 days later in four. Six dogs were studied under conditions of osmotic diuresis at all of these intervals.

While the glomerular filtration rate (GFR) appeared to remain constant throughout the 56 days of this study, abnormalities in renal tubular function were evident within 24 hours after irradiation. In water diuresis, free water clearance (C_{H_2O}) was significantly greater 1 day after exposure, averaging 0.88 ± 0.23 ml/min (SE) from the control kidney (CK) and 1.34 ± 0.31 ml/min from the irradiated kidney (IK) ($p < 0.005$). These differences became greater over the intervals studied and were independent of changes in GFR. Fractional excretion of sodium was also greater from the IK within a day of exposure, averaging 0.37 ± 0.11 percent from the CK and 0.54 ± 0.18 percent from the IK ($p < 0.005$). Such differences persisted in the same degree throughout the interval of the study. When vasopressin was infused, urine flow (V) fell significantly at all intervals studied postirradiation. However, V was significantly greater 24 hours after radiation exposure, averaging 0.36 ± 0.08 and 0.54 ± 0.10 ml/min from the CK and IK respectively ($p < 0.001$). This difference in V correlated well with a marked increase in the excretion of total solute and sodium. By day 14,

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urine flow from the irradiated kidney was not different from the control kidney. Twenty-eight days following exposure, V from the IK tended to be greater than from the CK. These differences were associated with a significant decline in negative free water clearance ($T^c_{H_2O}$) from the IK (0.30 ± 0.08 ml/min) when compared to the CK (0.52 ± 0.08 ml/min, $p < 0.01$).

The tubular maximum for $T^c_{H_2O}$ ($Tm^c_{H_2O}$) was determined in six dogs that were studied while undergoing a brisk osmotic diuresis and being infused with vasopressin. There was a significant decline in $Tm^c_{H_2O}$ 21 days after exposure which became more marked by day 28, averaging 1.18 ± 0.10 ml/min from the CK and 0.015 ± 0.13 ml/min ($p < 0.001$) from the IK.

When urine was collected 18-24 hours after complete food and water deprivation, no differences were seen in osmolality until day 21. By day 28, osmolality of urine collected from the IK was half that obtained from the CK, averaging 930 ± 148 and 1898 ± 259 mosmol/liter, respectively.

Thus the earliest effects of radiation are related to the ability of the proximal tubule to reabsorb sodium and are manifested by both an increase in the fractional and absolute excretion of sodium within 24 hours of exposure, which continues throughout the interval of the study, and by a marked increase in the excretion of C_{H_2O} within a day of exposure, which becomes greater with time. Approximately 3 weeks postexposure, but before GFR declines, the concentrating segment of the nephron is impaired. These studies suggest that renal tubular injury is the major early effect of radiation.

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